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INTERMITTENT FASTING: UNVEILING THE THERAPEUTIC POTENTIAL IN METABOLIC HEALTH MANAGEMEN - A LITERATURE REVIEW

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Abstract

With the global prevalence of obesity and metabolic syndrome increasing, innovative therapeutic strategies are needed to reduce this prevalence. One approach being explored is Intermittent Fasting. This study aims to evaluate the effectiveness of Intermittent Fasting in managing Metabolic Syndrome, obesity, type 2 diabetes mellitus (T2DM), and cardiovascular risk factors. Literature searches were conducted for the period from 2010 to 2023. The analysis focused on randomized controlled trials, clinical studies, case reports, case series, and review articles assessing the effects of Intermittent Fasting on metabolic syndrome. It was found that Intermittent Fasting contributes to weight loss, improved insulin sensitivity, and modulation of leptin and adiponectin levels. Although some studies show results similar to traditional calorie restriction, Intermittent Fasting has shown potential in improving lipid profiles and reducing blood pressure. Despite its promising potential, the implementation of Intermittent Fasting in clinical practice requires a deeper understanding of its mechanisms. Furthermore, additional research is needed to evaluate the feasibility of adopting Intermittent Fasting as a lifestyle. Intermittent Fasting shows benefits in managing obesity, metabolic syndrome, and cardiovascular risk factors.

***Keywords**: Intermittent fasting, metabolic syndrome, glucose disorder, cardiovascular diseases, weight loss*

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INTRODUCTION

With the rising global prevalence of obesity and metabolic syndrome, the medical community is intensifying its efforts to develop new therapeutic strategies to mitigate their pathophysiological impacts. Despite significant advancements in creating new medical treatments for obesity, there is an increasing trend towards enhancing dietary patterns through various nutritional regimens. Among these, intermittent fasting (IF) has emerged as a prominent approach, often recommended by health professionals due to its positive effects on weight management, heart health, and reducing oxidative stress.(Ginsberg & MacCallum, 2009; Naous et al., 2023)

Intermittent fasting involves alternating periods of eating and fasting, which can be structured in various ways. The most common methods include the 16/8 method (16 hours of fasting and 8 hours of eating), the 5:2 diet (eating normally for five days and restricting calories for two non-consecutive days), and the eat-stop-eat method (24-hour fasts once or twice a week). This eating pattern is not just a diet but a lifestyle change that shifts the focus from what you eat to when you eat.(Çerman et al., 2016; Gersing et al., 2023)

The primary benefit of IF is weight loss. By reducing the eating window, IF naturally lowers caloric intake, which can lead to weight loss. Additionally, fasting periods enhance hormone function to facilitate weight loss. For instance, fasting lowers insulin levels, which makes stored body fat more accessible for energy. Human growth hormone (HGH) levels increase, promoting fat loss and muscle gain. Norepinephrine (noradrenaline) levels rise, which can boost metabolism.(Al-Ghamdi & Rehman, 1998; Ottestad et al., 2018) This review article aims to provide a comprehensive overview of the impact associated with metabolic syndrome, explore the various forms of Intermittent Fasting, and present a brief summary of existing research on the impact of Intermittent Fasting on the fundamental components of metabolic syndrome.

METHOD

Comprehensive literature search was conducted to gather information on the effects of Intermittent Fasting on metabolic processes. The search platforms included PubMed, MEDLINE, and Google Scholar, spanning from 2010 to 2021. The focus was on various publications such as randomized controlled trials, clinical trials, case reports, case series, and review articles. Keywords used for the search were "Intermittent Fasting, Weight Disorders, Glucose Level Disorders, Cardiovascular Disorders, Metabolic Syndrome." The inclusion criteria for the articles were publications available in full-text format, written in English or Indonesian, and already published. Exclusion criteria were identical or duplicated journals, abstracts only, unpublished works, and those not relevant to the specified topic.

LITERATURE REVIEW

Nutrition In Metabolic Syndrome

Metabolic syndrome is characterized by a collection of metabolic abnormalities including central obesity, insulin resistance, hypertriglyceridemia, hypercholesterolemia, hypertension, and reduced high-density lipoprotein (HDL) levels. Additionally, it is associated with various secondary health issues such as pro-inflammatory and prothrombotic states, non-alcoholic fatty liver disease (NAFLD), cholesterol gallstone disease, and reproductive dysfunctions. Metabolic syndrome is increasingly recognized as a significant contributor to the escalation of type 2 diabetes and cardiovascular diseases.(Fahed et al., 2022; Kaur, 2014; Rochlani et al., 2017) It affects approximately 22-35% of the population in the United States. Around 35% of American adults are diagnosed with prediabetes, and without medical intervention, 15-30% of these individuals are likely to develop type 2 diabetes mellitus (T2DM) within five years. The global incidence of T2DM is alarmingly rising, parallel to the increasing prevalence of obesity. Projections indicate that over 75% of the adult population in the U.S. will be overweight or obese by 2030, with about 25% exhibiting severe obesity, indicated by a body mass index (BMI) of $\geq$35 kg/m2.(Tabák et al., 2012; Wang et al., 2020) Cardiovascular diseases, according to World Health Organization data, account for nearly one-third of all global deaths annually, amounting to 17.9 million fatalities.(World Health Organization, 2023)

There are several modifiable factors including habits and conditions such as smoking, obesity, hypertension, lipid disorders, unhealthy diet, sedentary lifestyle, and diabetes. Effective management of these factors can significantly reduce mortality rates. Lifestyle modifications like quitting smoking, increasing physical activity, and maintaining a healthy body weight are proven to lower the risk of cardiovascular diseases. As the global obesity crisis intensifies, the importance of dietary changes as a key modifiable aspect has emerged, sparking ongoing research into new dietary strategies aimed at calorie and body mass reduction to mitigate the prevalence of metabolic syndrome.(Ghodeshwar et al., 2023; Sharifi-Rad et al., 2020) Various dietary patterns have been scrutinized for their impact. The Western diet, characterized by high consumption of red meat, processed foods, refined sugars, and saturated fats, is linked with an increased risk of developing metabolic syndrome. On the other hand, the DASH diet, focused on hypertension control, has shown efficacy in reducing blood pressure and cardiovascular risk factors, though its direct impact on metabolic syndrome requires further observation. The Nordic diet, rich in vegetables, fruits, mushrooms, and fish, was evaluated in a randomized controlled trial involving adults with metabolic syndrome, showing significant improvements in lipid profiles, but no substantial changes in BMI, insulin sensitivity, and blood pressure. Lastly, the vegan diet, exclusively plant-based, has not been extensively studied in large-scale trials concerning metabolic syndrome.(Cena & Calder, 2020)

Intermittent Fasting Methods

Various methods of Intermittent Fasting are currently practiced. Standard methods include fasting for 24 hours alternately each day, and the 5:2 method, which involves a 24-hour fast twice a week combined with a very low-calorie diet on two other days, either consecutively or non-consecutively. Another common approach is time-restricted feeding, where fasting occurs daily for variable durations, typically within a 6-hour eating window, including breakfast in the morning and dinner before 3 pm, resulting in a 14-18 hour fast.(Vasim et al., 2022) Literature suggests that the inherent circadian rhythm is a primary mechanism for maintaining metabolic homeostasis. This rhythm, over a 24-hour period, coordinates the balance between anabolic and catabolic activities. The daily eat-fast cycle is crucial for maintaining the balance of mRNA and proteins, thus controlling various aspects of metabolism such as glycolysis, protein synthesis, lipid synthesis and oxidation, gluconeogenesis, and mitochondrial activities. Disruptions in the alignment between circadian timing and dietary intake patterns can lead to disturbances in the metabolic system, including increased oxidative stress, insulin resistance, and hormonal secretion disorders.(Kim & Lazar, 2020)

Mouse model studies have underscored the importance of Intermittent Fasting in maintaining a healthy circadian rhythm, which regulates metabolic processes. Time-restricted eating provides a consistent fasting period daily, helping to mitigate circadian rhythm disruptions and improve metabolic balance. In animal models, time-restricted eating has positively influenced various organ systems and prevented glucose intolerance, fatty liver, and dyslipidemia. A study by Chaix et al. also revealed the beneficial effects of time-restricted feeding on mouse metabolism. Human studies, although small in scale, have also shown the significance of time-restricted eating patterns in maintaining healthy metabolism. These studies have echoed the benefits observed in animal research, with time-restricted eating leading to reductions in energy intake, body weight, body fat, blood pressure, blood glucose, triglycerides, glucose tolerance, and inflammatory markers.(Chaix et al., 2014)

Intermittent Fasting Mechanism

In assessing the health effects of Intermittent Fasting, it is crucial to understand the fundamental physiology of glucose and lipid metabolism, especially the concept of "metabolic switching" that occurs during fasting.(Vasim et al., 2022) In 1963, Randle and colleagues introduced the "glucose-fatty acid cycle" theory, describing the competitive oxidation of glucose and fatty acids during eating and fasting. This cycle consists of four stages: the fed state, the post-absorptive or early fasting state, the fasting state, and the long-term fasting or starvation state. During the day, most tissues primarily use glucose for energy. Post-meal, glucose is utilized for energy, and excess fat is stored as triglycerides in adipose tissue. These triglycerides are then broken down into fatty acids and glycerol for energy during extended fasting. The liver converts these fatty acids into ketone bodies, which become a significant energy source during fasting, particularly for the brain. During Intermittent Fasting, individuals typically experience the fed, post-absorptive, and fasting states. Insulin dominates the fed state, promoting glucose utilization, while glucagon takes over in the fasting state, utilizing liver glycogen stores. The metabolic switch, marking the shift from glucose to fatty acid-derived ketones as the primary energy source, typically occurs after 12 hours of no food intake. This switch is an evolutionary mechanism transitioning metabolism from lipid/cholesterol synthesis and fat storage to fat mobilization through fatty acid oxidation and ketone production, thereby preserving muscle mass and function. It is hypothesized that Intermittent Fasting regimens that trigger this switch can enhance body composition in overweight individuals.(Muoio et al., 2012; Vasim et al., 2022)

In a regular diet with three meals and snacks, the metabolic switch is never activated, keeping ketone levels low and glucose usage high. Conversely, in complete alternate-day fasting, ketones progressively increase, and glucose levels remain low on fasting days, with opposite trends on eating days. In a pattern where all food is consumed within a 6-hour window, the metabolic switch is activated during the subsequent 12 hours of fasting and remains active for about six hours each day until the next meal. Metabolic switching through Intermittent Fasting leads to enhanced metabolism, extended health span, and increased longevity through several mechanisms. These include the activation of AMP-activated protein kinase (AMPK), inhibiting anabolic pathways and stimulating catabolic reactions like autophagy, enhancing mitochondrial function. Fasting reduces carbohydrate intake, depletes liver glycogen, mobilizes fatty acids, and increases ketone production, especially β-hydroxybutyrate. This process activates the NAD+ deacetylase activity in sirtuins, leading to autophagy and reduced oxidative stress. Furthermore, free fatty acids activate transcription factors such as PPAR-α and ATF4, leading to the production of fibroblast growth factor 21 (FGF21), which has extensive effects on various cells and brain functions. β-hydroxybutyrate also serves as a signaling molecule, activating transcription factors and promoting the expression of brain-derived neurotrophic factor (BDNF) in neurons.(Anton et al., 2018; Vasim et al., 2022)

In clinical research, Intermittent Fasting regimens have primarily been explored for counteracting obesity and enhancing health by mitigating the progression of cardiovascular disease, metabolic syndrome, hypertension, and type 2 diabetes mellitus. However, there is a lack of long-term comparative studies to determine the long-term efficacy of these dietary protocols.(Vasim et al., 2022) The subsequent review will focus on the current literature examining the various effects of Intermittent Fasting on weight loss, insulin resistance, cardiovascular parameters, and oxidative stress/inflammation.

Intermittent Fasting And Weight Loss

Visceral adipose tissue is a crucial player in the body's metabolic processes, functioning as both a paracrine and endocrine organ through the secretion of adipokines. These adipokines can be pro-inflammatory, such as leptin, or anti-inflammatory, like adiponectin. Leptin regulates body weight by modulating signals to the hypothalamus and other brain regions, suppressing food intake and increasing energy expenditure. Conversely, Adiponectin interacts with various receptors to enhance fatty acid oxidation in skeletal muscles and the liver, reduce hepatic gluconeogenesis, and increase glucose uptake. Notably, adiponectin levels decrease as visceral fat accumulates. The beneficial effects of Intermittent Fasting, particularly in addressing obesity, are partially attributed to the metabolic shift from glucose to fatty acids and ketones as the primary fuel source during fasting periods. Intermittent Fasting has effectively reduced adiposity, especially in visceral and truncal fat, even with relatively minor energy deficits. This reduction in adiposity can lead to improved leptin/adiponectin levels and sensitivity, ultimately enhancing appetite control.(Deng & Scherer, 2010; Ramos-Lobo & Donato, 2017; Song & Kim, 2023)

In a study by Trepanowski et al., conducted in 2017, the effects of alternate-day fasting were compared with daily calorie restriction in terms of weight loss, weight maintenance, and cardiovascular disease risk indicators. This randomized clinical trial involved obese adults, aged 18 to 64 with an average body mass index of 34, at a single-centre academic institution in Chicago. Participants were assigned to one of three groups for a year: alternate-day fasting (consuming 25% of energy needs on fast days and 125% on alternating “feast days”), daily calorie restriction (75% of energy needs every day), or a no-intervention control group. The primary outcome assessed was the change in body weight, while secondary outcomes included adherence to the dietary intervention and cardiovascular disease risk indicators. Over 12 months, the control group maintained their baseline weight, whereas both the alternate-day fasting and daily caloric restriction groups showed a weight decrease of 7% below baseline at 6 months, before experiencing some weight regain, ending at approximately 4.5% below starting weight after 12 months. The alternate-day fasting group had a higher dropout rate of 38%, compared to 29% in the daily calorie restriction group and 26% in the control group. Ultimately, the study concluded that alternate-day fasting did not offer additional health benefits over standard calorie restriction.(Trepanowski et al., 2017)

Intermittent Fasting And Glucose Disorders

The development of insulin resistance, a key feature in metabolic disorders, is believed to be influenced by several mechanisms. One notable theory suggests that increased adiposity leads to chronic inflammation, which subsequently causes insulin resistance in various tissues. Intermittent Fasting can potentially reduce adiposity and the associated insulin resistance by limiting caloric intake and inducing metabolic reprogramming. Another hypothesis posits that reduced energy intake, such as that achieved through Intermittent Fasting, could lead to a prolonged decrease in insulin production and increased levels of AMP-activated protein kinase (AMPK), contributing to improvements in insulin sensitivity and glucose homeostasis.(Vasim et al., 2022)

A study conducted by Halberg et al. examined the impact of Intermittent Fasting on insulin sensitivity. The study involved eight healthy young men with an average body mass index (BMI) of 25.7, who underwent Intermittent Fasting for 20 hours on alternate days for two weeks, maintaining consistent physical activity. The study found that while weight loss was not significant, insulin sensitivity improved. This was evidenced by increased glucose infusion rates and whole-body glucose uptake rates during hyperinsulinemia clamp studies, as well as a more pronounced inhibition of adipose tissue lipolysis and an increase in adiponectin levels following fasting periods. This research was among the first to demonstrate that Intermittent Fasting can enhance insulin-mediated glucose uptake.(Halberg et al., 2005)

Numerous clinical trials have investigated the effects of Intermittent Fasting on insulin sensitivity, employing various approaches such as alternate-day fasting, alternate-day modified fasting, and the 5:2 method. These studies generally indicate improvements in insulin sensitivity and reductions in dyslipidemia, although not all reported these findings.(Patterson et al., 2015)

A particularly interesting study by Sutton et al. investigated the effects of Intermittent Fasting, specifically time-restricted feeding (TRF), on insulin sensitivity, independent of weight loss. This five-week, randomized, crossover, controlled feeding trial involved men with prediabetes and tested TRF (a 6-hour daily eating period with dinner before 15:00) against a standard 12-hour eating period. The study primarily focused on glucose tolerance, postprandial insulin, and insulin sensitivity, assessed through a 3-hour oral glucose tolerance test (OGTT). While TRF did not significantly affect fasting glucose or glucose levels during the OGTT, it did result in reduced fasting insulin levels and decreased insulin levels at specific post-load time points. TRF also improved β cell responsiveness and decreased insulin resistance. Although TRF did not significantly improve glucose levels, it substantially lowered insulin levels and enhanced insulin sensitivity and β cell function, aligning with other clinical trials suggesting the efficacy of Intermittent Fasting in reducing plasma insulin and increasing insulin sensitivity more than lowering glucose levels.(Sutton et al., 2018)

Carter and colleagues conducted a substantial 52-week study to evaluate the impact of Intermittent Fasting compared with continuous energy-restricted diet on glycemic control in patients with Type 2 Diabetes Mellitus (T2DM). The study encompassed 137 participants with obesity and T2DM, averaging an age of 61 years and a baseline HbA1c of 7.3%. Participants were assigned to either a 5:2 intermittent energy restriction group (500-600 kcal/day for two days per week) or a continuous energy restriction group (1200-1500 kcal/day). After 12 months, both groups exhibited similar reductions in HbA1c levels, with the Intermittent Fasting group experiencing a more significant weight loss.(Carter et al., 2018)

Intermittent Fasting And Cardiovascular Diseases

Insulin resistance is closely associated with increased inflammation, elevated C-reactive protein levels, decreased adiponectin, smaller low-density lipoprotein (LDL) particle size, and other metabolic factors. These collectively contribute to or correlate with the development of atherosclerosis and coronary artery disease.

Moreover, insulin itself, beyond its association with atherogenic dyslipidemia, also elevates the risk of fluid retention and congestive heart failure. Therefore, reducing insulin levels through Intermittent Fasting could potentially lower the incidence of major adverse cardiac events. Recent studies have explored the mechanisms by which Intermittent Fasting may improve blood lipid profiles. It has been demonstrated that nuclear expression of peroxisome proliferator-activated receptor-α and peroxisome proliferator-activated receptor γ coactivator 1 α in the liver leads to increased fatty acid oxidation and Apo A production while simultaneously reducing ApoB synthesis. These physiological changes potentially decrease serum levels of VLDL, LDL-C, and small dense LDL-C.(Ellulu et al., 2017; Vasim et al., 2022)

The reduction in blood pressure associated with Intermittent Fasting might relate to the activation of the parasympathetic system, driven by enhanced activity of the cholinergic neurons in the brainstem. While brain-derived neurotrophic factor (BDNF) is typically produced in response to glutamatergic receptor activation, Intermittent Fasting has been identified as a key environmental stimulus. Adiponectin levels decrease during various pathological processes, including atherosclerosis, insulin resistance, Type 2 Diabetes Mellitus (T2DM), and coronary disease. Intermittent Fasting induces increased secretion of adiponectin from adipocytes. Adiponectin exhibits anti-atherosclerotic and anti-inflammatory properties, inhibiting monocyte adhesion to endothelial cells and the release of vascular cell adhesion molecule 1 (VCAM-1), endothelial-leukocyte adhesion molecule 1 (ELAM-1), and intracellular adhesive molecule 1 (ICAM-1) on vascular endothelial cells, thus reducing local and systemic inflammation.(Kodela et al., 2023)

While research on the effects of Intermittent Fasting on cardiovascular parameters shows promising results, it is essential to recognize the current literature's limitations. These include small sample sizes and a lack of randomized study designs, meta-analyses, or systematic reviews. Additionally, most randomized controlled trials (RCTs) exclude patients with Type 1 Diabetes Mellitus, who might also benefit from such interventions. This gap underscores the need for further research, particularly studies that incorporate diabetes technology to minimize adverse effects and long-term follow-up studies to assess the sustainability of Intermittent Fasting as a lifestyle choice. Moreover, patient adherence remains a challenge and must be considered when designing research protocols.

INTERMITTENT FASTING AND LIFESTYLE

This review highlights the potential benefits of Intermittent Fasting on metabolic health, yet integrating such a dietary approach into everyday life is a pertinent concern. The practicality of fasting, especially in a modern lifestyle, can be challenging. However, Intermittent Fasting's adaptability, considering its various protocols, potentially makes it more manageable than other restrictive diets like ketogenic, vegan, or daily caloric restriction. Additionally, the alignment of Intermittent Fasting with natural circadian rhythms suggests it might be a more physiologically attuned diet option. To assess the applicability of time-restricted eating in preventing lifestyle-dependent diseases among working populations, Tinsley et al. conducted a study. Their findings indicated that this eating pattern is not only feasible but also conducive to an improved quality of life. Wegman et al. explored the practicality of Intermittent Fasting in humans. Participants in their study demonstrated adherence to the Intermittent Fasting dietary pattern, as per the study's surveys. Generally, Intermittent Fasting strategies have been observed to be relatively practical in daily life for enhancing metabolic health.(Vasim et al., 2022)

However, existing research on the feasibility of Intermittent Fasting within the modern lifestyle is limited. Therefore, further research is essential, focusing on how Intermittent Fasting interacts with individual social influences, environmental factors, and unique physiological aspects. Future research should ideally delve into a broader range of factors influencing an individual’s ability to sustain Intermittent Fasting as part of their regular lifestyle.

CONCLUSION

Intermittent Fasting has garnered significant attention for its positive impact on weight management, insulin resistance, and the modulation of leptin and adiponectin levels. Both preclinical and clinical research have highlighted its potential benefits across various conditions such as obesity, Type 2 Diabetes Mellitus (T2DM), hypertension, and in enhancing cardiovascular risk factors. However, a critical perspective on Intermittent Fasting arises from observations that, despite robust animal study data, many clinical trials have not demonstrated significantly greater improvements with Intermittent Fasting compared to traditional caloric restriction. The absence of extensive randomized controlled trials (RCTs) specifically examining the efficacy and potential side effects of Intermittent Fasting in individuals with metabolic syndrome, prediabetes, and T2DM over extended periods adds to this uncertainty. This gap in research makes it challenging to accurately determine the risk-to-benefit ratio of various Intermittent Fasting regimens. There is a clear need for studies that assess both the short-term benefits and potential drawbacks of Intermittent Fasting and examine its long-term efficacy as a sustainable lifestyle approach. While Intermittent Fasting shows promise as a therapeutic intervention for metabolic health, its superiority over other dietary approaches remains to be conclusively established. Future research, particularly long-term RCTs involving diverse populations with metabolic syndrome, prediabetes, and T2DM, will be crucial in evaluating Intermittent Fasting's role in managing these conditions and its viability as a long-term lifestyle modification.

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